REMARKS

Claims 1-3, 5, 7-12, 19, 24 and 26-28 are pending in the application. The specification of the application has been amended to include the section heading "Government Support" and to correct typographical errors. Claim 20 has been canceled. Claims 1, 5 and 7 have been amended. Claim 1 has been amended to recite only covalent binding of the reactive group to the tissue or cellular surface and that the delivery steps can be affected under conditions tolerable *in vivo*. Support for the added language contained in claim 1 is found in claim 20, now canceled. Claim 7 has been amended to recite that the reactive group in the molecule N-hydroxy-succinimide-biotin (NHS-biotin) is N-hydroxy-succinimide. Support for the language "NHS-biotin" contained in claim 7 is found at page 6, line 17 of the specification. Claim 5 has been amended to correct a typographical error. No new matter has been added. In view of the foregoing amendments and following evidence and remarks, Applicants believe that all the asserted rejections are in condition for withdrawal and that all pending claims 1-3, 5, 7-12, 19, 24 and 26-28 are in condition for allowance.

35 U.S.C. § 112 Rejection

Claims 1-3, 5, 7-12, 19, 20, 24 and 26-28 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the reasons set forth in the previous Office Action. The Examiner acknowledges that the invention is enabled for a two-step delivery of a chemical or biological entity to an isolated vascular tissue (either *in vitro* or *in situ*) but asserts that the invention is not enabled for a method for the delivery of any target tissue or cellular surface of a patient (which includes *in vivo*) as claimed. The Examiner further asserts that post-filing art teaches that problems remain with respect to endogenous biotin blocking the biotin-binding sites of streptavidin.

The claimed invention is directed to a method for delivering a chemical or biological entity to a target tissue or cellular surface of a patient. The method comprises binding a molecule, comprised of at least one reactive group that reacts with groups on the tissue or cellular surface of a patient *in vivo* and at least one signaling molecule. The chemical or biological entity attaches to the signaling molecule by means of a recognition molecule, in which the recognition molecule specifically recognizes the signaling molecule due to the affinity that the recognition molecule and the signaling molecule have for each other. Additionally, the reactive group binds covalently to the tissue or cellular surface.

Contrary to the Examiner's assertion that the invention is not enabled for a method of delivering a chemical or biological entity to any target tissue or cellular surface of a patient *in vivo*, Applicants submit that the claimed invention provides more than adequate enablement for one skilled in the art to practice the invention without undue experimentation. Fortunately, the Examiner does not have to accept this conclusion on its face because supporting investigative data, which provides evidence and corroboration for these conclusions, are submitted herewith.

Accompanying this Amendment is the signed Declaration of William R. Wagner, Ph.D. The declarant, William R. Wagner, Ph.D., is a citizen of the United States and resides at 10193 Sudberry Drive, Wexford, PA 15090. Dr. Wagner graduated from The Johns Hopkins University in 1986 with a B.S. in Chemical Engineering and graduated from The University of Texas at Austin in 1991 with a Ph.D in Chemical Engineering. From September, 1986 to March, 1991, Dr. Wagner was a research associate in the Department of Chemical Engineering at The University of Texas at Austin. From September, 1996 to June 1999, Dr. Wagner was a member of the core faculty in the Department/Program of Bioengineering at the University of Pittsburgh, an Assistant Professor of Chemical Engineering in the Department of Chemical Engineering at the University of Pittsburgh and an Assistant Professor of Surgery in the Department of Surgery at the University of Pittsburgh. From July, 1999 to December, 2006, Dr. Wagner was employed as an Associate Professor of Bioengineering and Chemical Engineering in the Departments of Bioengineering and Chemical Engineering at the University of Pittsburgh and an Associate Professor of Surgery (tenured) in the Department of Surgery at the University of Pittsburgh. Since 2001, Dr. Wagner has served as a Deputy Director of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh and since December 2006, he has been employed as Professor of Surgery, Bioengineering and Chemical Engineering at the University of Pittsburgh. A copy of Dr. Wagner's curriculum vitae is attached herewith as Exhibit A.

Dr. Wagner, as an expert in the field of biomedical engineering, attests, in Paragraph 3 of the Declaration, that not only would one skilled in the art would be able to practice the claimed invention with respect to a two-step delivery of a chemical or biological entity to an *in vitro* or *in situ* isolated vascular tissue, but also would be able to practice the claimed method with respect to specifically delivering a chemical or biological entity to any target tissue or cellular surface of a patient *in vivo*.

To corroborate Dr. Wagner's attestations, as described in Paragraph 4 of the Declaration, a scientific investigation was conducted involving the use of a protein-reactive

polymer to modify injured vascular surfaces for the purpose of blocking thrombosis and providing a site for the targeted delivery of microspheres as models of therapeutic agents. A copy of a paper reporting this investigation is attached hereto as Exhibit B. The study involved employing a protein-reactive polymer to modify injured vascular surfaces for the purpose of blocking thrombosis and providing a site for the targeted delivery of therapeutics. N-hydroxysuccinimide-polyethylene glycol biotin (NHS-PEG biotin) was used to covalently modify vascular surfaces in an *in vivo* rabbit femoral artery model of vascular injury. The NHS reactive group covalently linked with primary amines, with the most accessible being the epsilon amine found on the amino acid lysine. A stable amide bond was formed, covalently linking the protein-reactive polymer with a primary amine of a protein on a vascular surface.

As described in Paragraph 5 of the Declaration, the above-described investigation showed that NeutrAvidin-coated microspheres preferentially adhered to balloon-injured arteries modified by PEG-biotin as opposed to balloon-injured, unmodified vascular surfaces *in vivo* at all time points evaluated. Microspheres are representative of a particulate drug or carrier that can be loaded with various therapeutics designed to treat various ailments in a patient.

The investigation also evaluated the ability of using the same targeting strategy to target agents to healthy vascular tissue, which could be employed to deliver chemotherapeutics to tumor vasculature, in addition to the targeting of pharmaceuticals to sites of vascular injury. The study revealed that, as was the case with targeting balloon-injured arteries, the NeutrAvidin-coated microspheres preferentially targeted healthy vascular tissue that was modified with polymer as opposed to unmodified arteries.

With respect to the Examiner's assertion that post-filing art teaches that problems remain with respect to endogenous biotin blocking the biotin-binding sites of streptavidin, the declarant attests, at Paragraph 7 of the Declaration, that the investigation clearly demonstrates the ability to provide site-specific recognition signals for delivery of chemical and biological entities, as claimed in independent claim 1, to healthy and damaged tissues. Furthermore, the investigation also demonstrates that chemical and biological entities can be delivered to healthy and damaged tissues without encountering problems with endogenous biotin blocking the biotin-binding sites of streptavidin.

The declarant further attests, at Paragraph 8 of the Declaration, that the results of this investigation clearly demonstrate that healthy and injured vascular segments can be modified *in vivo* in a patient. Hence, the declarant states that, as one skilled in the art confronted with

the disclosure of the instant application, he would unquestionably be able to practice the claimed invention, as would others who are skilled in the art, as set forth in claims 1-3, 5, 7-12, 19, 24 and 26-28, without undue experimentation.

Based on the foregoing evidence provided in the above-described expert's Declaration, Applicants respectfully submit that the claimed invention provides more than adequate enablement for one skilled in the art to practice the invention in patients *in vivo* without undue experimentation, and thus request withdrawal of this rejection.

35 U.S.C. 112 Rejection

Claims 1, 2 and 7-9 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserts that the claims recite the use of NHS as the reactive group. However, the art does not teach the use NHS *per se*, and thus it is irrelevant whether one skilled in the art would recognize that the recitation "NHS" means "NHS-biotin."

Applicants point out that claim 7 is the only claim which recites using NHS as the reactive group. Claim 7 has been amended to recite "N-hydroxy-succinimide-biotin (NHS-biotin)," support for which is contained at page 6, line 17 of the specification. Applicants submit that claim 7 as amended obviates this rejection and request withdrawal of the rejection of claims 1, 2 and 7-9.

35 U.S.C. § 102 Rejections

Claims 1, 10-12, 20 and 24 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Saga et al. for the reasons set forth in the previous Office Action. The Examiner acknowledges that Saga et al. do not teach covalent binding but do teach non-covalent binding. Claim 1 has been amended to delete the recitations "ionically" and "non-covalently." Claim 20 has been canceled. Thus, claim 1 as amended only recites "covalently." The features of dependent claims 10-12 and 24 are not asserted as independently establishing patentability apart from the claim or claims from which they depend. Applicants respectfully submit, therefore, that claim 1 as amended, and claims 10-12 and 24, which depend either directly or indirectly from claim 1, are not anticipated by Saga et al. and thus request withdrawal of this rejection.

Claims 1, 5, 7, 9-11, 19, 24 and 28 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Wojda et al. for the reasons set forth in the previous Office Action.

Claim 1 has been amended to include the recitations recited in claim 20, now canceled, namely, that the delivery of the chemical or biological entity can be effected under conditions tolerable *in vivo*. Applicants point out that claim 20 is not asserted by the Examiner to be anticipated by Wojda et al. More importantly, Applicants point out that

Wojda et al. neither teaches nor suggests an *in vivo* delivery system of chemical or biological entities targeted to a tissue or cellular surface of a patient. The features of dependent claims 5, 7, 9-11, 19, 24 and 28 are not asserted as independently establishing patentability apart from the claim or claims from which they depend. Applicants respectfully submit, therefore, that claim 1 as amended, and claims 5, 7, 9-11, 19, 24 and 28, which depend either directly or indirectly from claim 1, are not anticipated by Wojda et al., and thus request withdrawal of this rejection.

35 U.S.C. § 103 Rejections

Claims 1, 2, 8, 10-12, 20 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Saga et al. in view of both Francis et al. and Kaiser et al. for the reasons set forth in the previous Office Action. The Examiner acknowledges that Saga et al. do not teach covalent binding but do teach non-covalent binding. Claim 1 has been amended to delete the recitations "ionically" and "non-covalently." Claim 20 has been canceled. Claim 1 as amended only recites "covalently." The features of dependent claims 2, 8, 10-12, 20 and 24 are not asserted as independently establishing patentability apart from the claim or claims from which they depend. Applicants respectfully submit, therefore, that claim 1 is neither taught nor suggested by Saga et al., Francis et al. or Kaiser et al., either alone or in combination. Because claims 2, 8, 10-12 and 24 depend either directly or indirectly from claim 1, they too are neither taught nor suggested by Saga et al. in view of both Francis et al. and Kaiser et al.

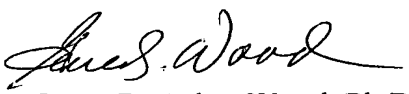
Claims 1, 10-12, 19, 20 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Saga et al. in view of both Chinol et al. and Wilbur et al. Here again, the Examiner acknowledges that Saga et al. do not teach covalent binding but do teach non-covalent binding. Claim 1 has been amended to delete the recitations "ionically" and "non-covalently." Claim 20 has been canceled. Claim 1 as amended only recites "covalently." The features of dependent claims 10-12, 19, 20 and 24 are not asserted as independently establishing patentability apart from the claim or claims from which they depend. Applicants respectfully submit, therefore, that claim 1 is neither taught nor suggested by Saga et al., Chinol et al. or Wilbur et al., either alone or in combination. Because claims 10-12, 19 and 24 depend either directly or indirectly from claim 1, they too are neither taught nor suggested by Saga et al. in view of both Chinol et al. and Wilbur et al.

Claims 1, 3, 10-12, 20 and 24 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Saga et al. in view of Muzykantov et al. Again, the Examiner acknowledges that Saga et al. do not teach covalent binding but do teach non-covalent

binding. Claim 1 has been amended to delete the recitations "ionically" and "non-covalently." Claim 20 has been canceled. Claim 1 as amended only recites "covalently." The features of dependent claims 3, 10-12, 20 and 24 are not asserted as independently establishing patentability apart from the claim or claims from which they depend. Applicants respectfully submit, therefore, that claim 1 is neither taught nor suggested by Saga et al. or Muzykantov et al., either alone or in combination. Because claims 3, 10-12 and 24 depend either directly or indirectly from claim 1, they too are neither taught nor suggested by Saga et al. in view of Muzykantov et al.

In view of the foregoing amendments and remarks, it is respectfully submitted that all pending claims 1-3, 5, 7-12, 19, 20, 24 and 26-28 in the present application comply with the requirements of Section 112 and are distinguishable from the cited prior art. Accordingly, reconsideration and withdrawal of the rejections and an early Notice of Allowance are respectfully requested.

Respectfully submitted,



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